Impact of the SARS-CoV-2 Pandemic on the Conduct of DCP Trials: *Update on TMIST – Tomosynthesis Mammographic Imaging Screening Trial*

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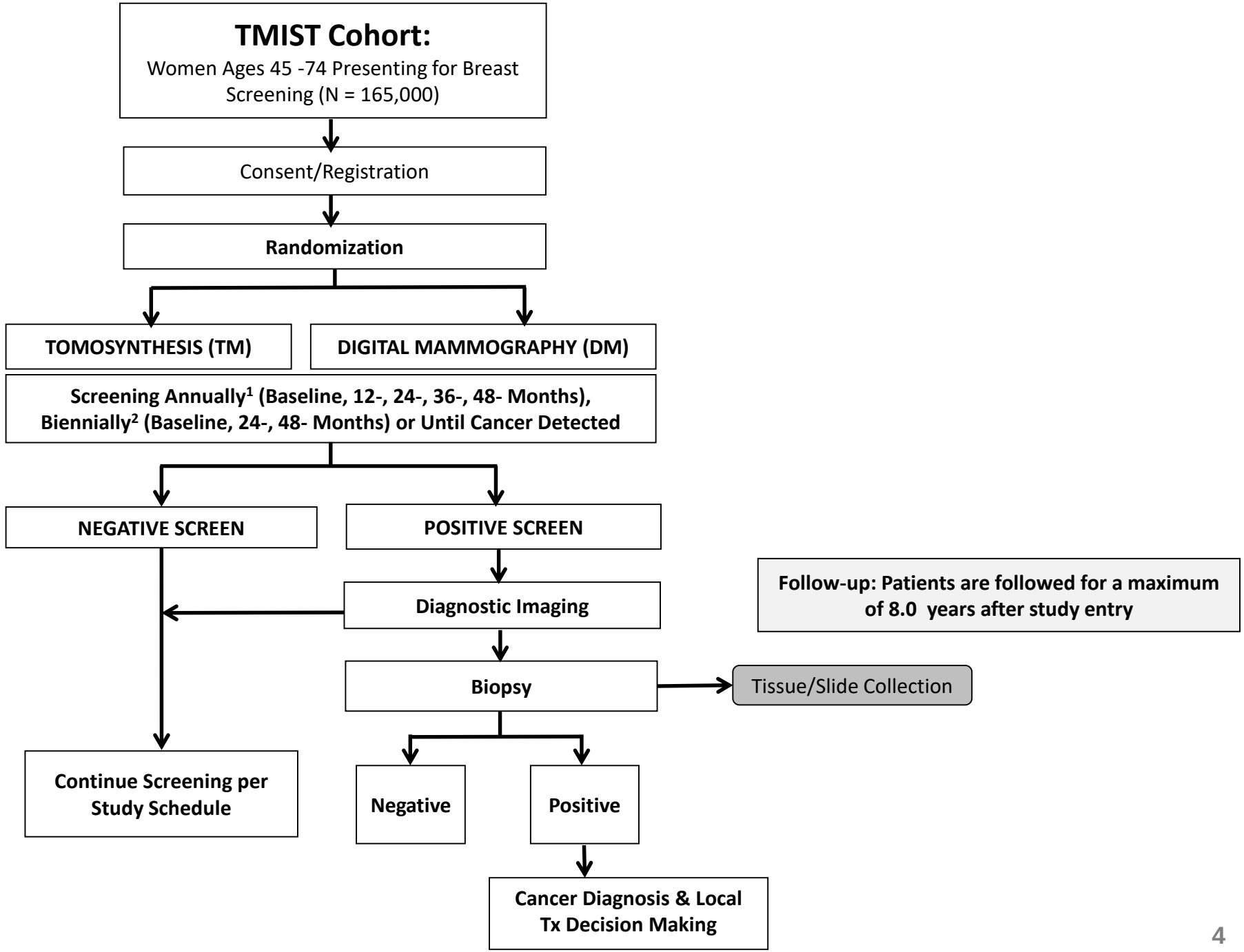
Introduction

- The pandemic has decreased accrual to our trials.
- As some of these trials take a long time to complete, it is important to ask if these trials are still poised to answer the critical research questions they were intended to address in a timely fashion.
- We consider on-going reviews of our prevention trials as our stewardship responsibility.
- Today I would like to focus on **TMIST,** DCP's largest trial.

Primary Aim and Summary of TMIST

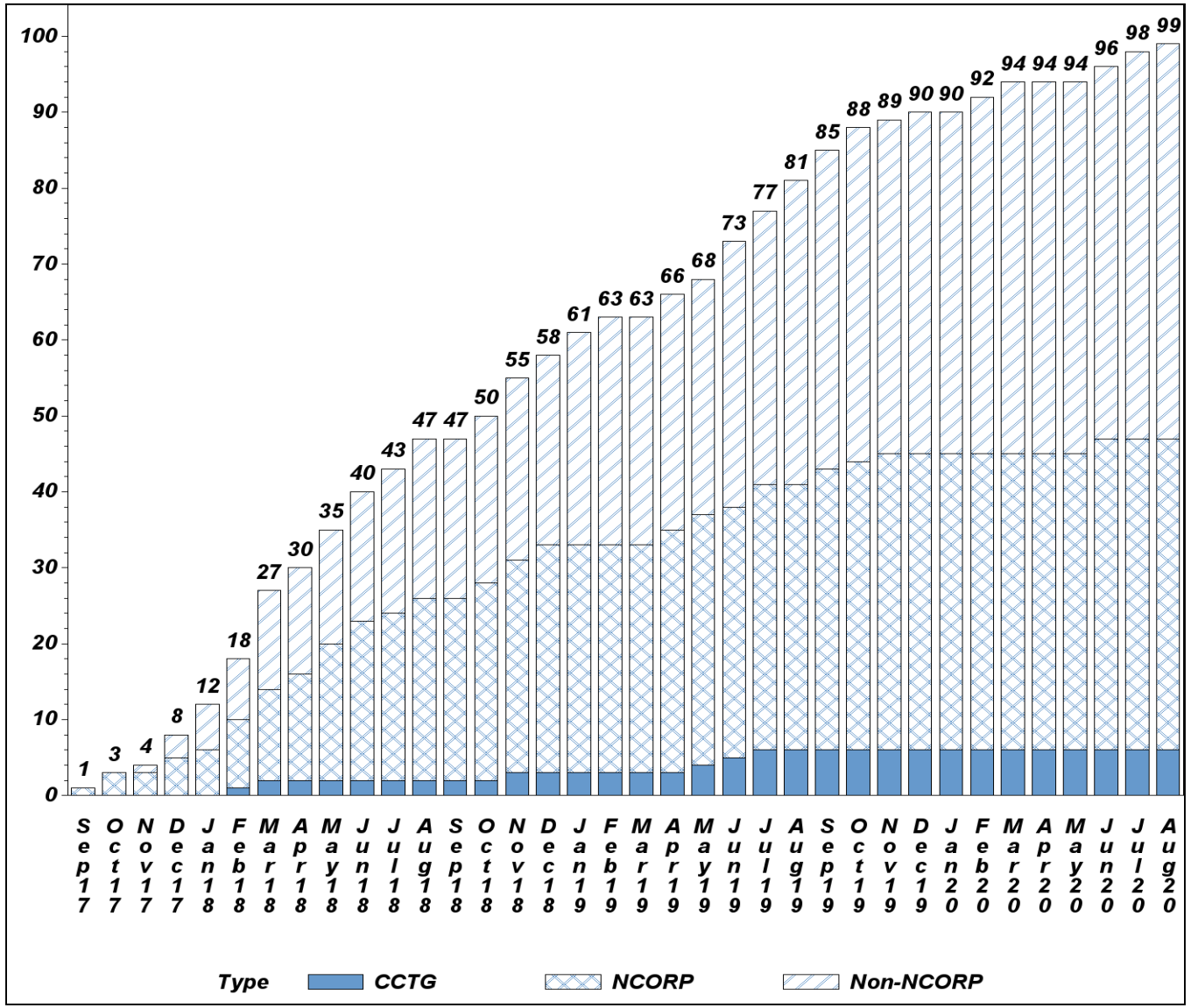
- To determine whether the cumulative rate of advanced breast cancer in women undergoing screening with tomosynthesis plus digital mammography (“3-D”) is reduced compared to digital mammography (“2-D”) alone.
- Advanced cancer is defined as any cancer diagnosed in the 4.5 years after study entry that is metastatic or a large tumor (based on subtype).
- Mortality is not the endpoint of TMIST.
- TMIST is being conducted at NCORP and non-NCORP sites and is being led by Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN) (ECOG-ACRIN).
- TMIST was originally projected to complete enrollment by 2020 (2.5 years of accrual) (5,500 per month) and to finish in 2025.
- Proposed Sample Size = 165K participants; current enrollment is <30K
- Estimated Costs for 2021-4: $93.9 Million

Study Design



Clinical Sites

- 112 sites are currently open to accrual in CTSU
- 99 sites have enrolled at least 1 participant
- 13 sites are currently open in CTSU but have no enrollments as of 9/1/2020
- 23 US sites and 3 international sites are in the process of submitting qualifications to activate TMIST

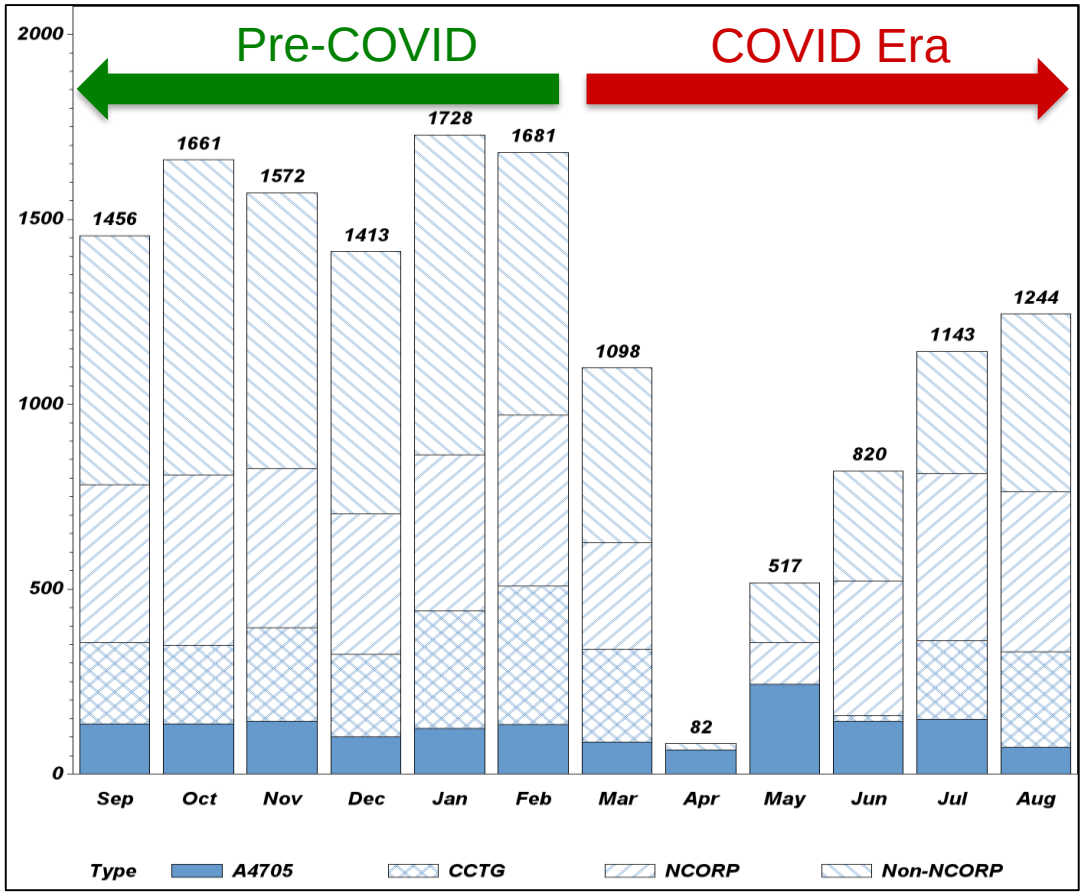


Accruals and the Impact of COVID

To Date:

- *Target Accrual*: 165K (Average ~5,500 per month) (completion of enrollment)
- *Actual Accrual*: <30K (Average <1,500 per month)
  - Maximum enrollment of ~1,700 (January & February of 2020)
  - Impact of COVID: ~50% reduction in enrollment (vs. 1,700 per month) for a 6-month period from March through August

Monthly Accrual for the Last 12 Months



TMIST Activation on July 6, 2017; 1st Accrual on September 28, 2017

Summary of the Evidence

- Meta-Analysis by Marinovich *et al*., JNCI, 2018:
  - *Single-Arm Studies.* 3-D detected more cancers but had a marginally higher recall compared to 2-D; and
  - *Two-Arm Studies (RCTs).* 3-D detected more cancers and had a lower recall compared to 2-D
- Observational Study by Lowry *et al*., JAMA, 2020:
  - 3-D detected more total and invasive cancers, resulted in more biopsies, but had fewer recalls than 2-D; and
  - 3-D had a lower recall-to-cancer and biopsy-to-cancer ratios compared to 2-D

Landscape Analysis of Ongoing Trials (from clinicaltrials.gov)

NCT	Study Title	N; Age Range (Years)	Start- End	Follow-Up	Locale
03377036	Breast Cancer Screening: Digital Breast Tomosynthesis Versus Digital 2D Mammography	80,000; 50-69	07/18- 07/23	2 Years	Germany
03733106	Prospective Trial of Digital Breast Tomosynthesis (DBT) Breast Cancer Screening	100,000; 50-70	12/18- 07/24	3 Years	UK
02835625/6	The Digital Breast Tomosynthesis Trial in Bergen - Part 1 & 2	~30,000; 48-71	01/18- 01/22	2 Years	Norway

Key Considerations:

- Under-accrual, compounded by the SARS-CoV-2 pandemic, will likely result in delayed outcomes and escalate costs; ECOG-ACRIN is adding sites but it is unclear if a 3,000-per-month accrual ever will be achieved (n.b., 2,000 per month has never been achieved).
- Relevance of the data by the completion of the trial is uncertain because:
  - 3-D market penetrance by the conclusion of the trial (68% of Certified Facilities have at least one 3-D Unit and 40% of all units are 3-D in 2020); and
  - Evidence is already available suggesting that 3-D is no worse and probably better than 2-D; and
  - Other trials and observational cohorts, while imperfect, will contribute additional, informative data.

Final Comments & NCAB Advice Sought

- As initially conceived, TMIST will not complete accrual until 2023 (if 3,500 enrolled per month) or 2026 (if 2,000 enrolled per month)(vs. mid-2020 completion). There could be further delays if there is a long-term impact of the pandemic.
- Follow-up (~5 years) and primary data analysis (~1 year) will add ~6 years after enrollment i.e., completion and reporting of the data between 2029 and 2032 (vs. 2025).
- Ongoing breast cancer screening trials will report their results well before then, and radiological practice likely will change substantially during that interval.
- We propose the creation of Working Group, reporting to **Clinical Trials and Translational Research Advisory Committee**, to examine the utility of TMIST given these unanticipated challenges due to the pandemic.